IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Norman Nashed

Serial No. 09/619,493 : Examiner: S. Qazi

Filed: July 19, 2000 : Group Art Unit: 1616

Title: **THERAPEUTIC GESTAGENS FOR THE TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER**

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 2231-1450

Sir:

I, Marie L. Foegh, being duly warned declared that:

I am a citizen of the United States, residing at 44 Adams Drive, Cresskill, NJ.

I possess the degrees of M.D. and D.Sc., having studied at University of Copenhagen Medical School, Copenhagen Denmark. I did postgraduate training

at University Hospitals and the University Department OB/GYN at Frederiksberg

Hospital in Copenhagen, Denmark. I also held a fellowship in the Department of Medicine at Georgetown University Medical Center, Washington, D.C.

I am currently a Clinical Professor of Medicine at Emory University Medical School in the Department of OB/GYN and Vice President of Female Healthcare

in Clinical Research at Berlex Laboratories in Montville, NJ.

Two publications have been cited as in the Office Action of July 27, 2004 with respect to patentability of PMDD methods, namely, Dennerstein, *et al.*,[1] and Cullberg.[2] In this declaration, that applicants will demonstrate the following:

1. Those two publications do not suggest PMDD treatments with oral contraceptives. In fact, they show that as of the date of their respective publications, the question of the impact of oral contraceptives on menstrual symptoms and mood was far from settled.

2. A sample of literature from the time period ranging from the time of the Dennerstein paper (1985) until the patent filing (2000) suggests that one skilled in the art would have been fairly certain that oral contraceptives were not at all useful against menstrual symptoms and mood.

Consequently, this declaration will conclude that there is no suggestion of treating PMDD based on the cited disclosures. This declaration will also conclude that if a person skilled in the art could come to an obvious conclusion as of the time of the patent filing, it would be that oral contraceptives do not work in treatment of PMDD. Therefore the applicants' finding is unexpected and patentable.

1. Evidence of the Two Publications

The Cullberg publication is chronologically the earlier of the two publications. In chapter 2 of this publication (pp. 10-18, including its table 2.1, pp. 12-13), a variety of

[1] L Dennerstein, C Spencer-Gardner, G Gotts, JB Brownk, MA Smith, GD Burrows, Progesterone and the premenstrual syndrome: a double blind crossover trial. *British Medical Journal*, **290**:1617—1621 (1 June 1985).

[2] J Cullberg, Mood Changes and Menstrual Symptoms with Different Gestagen/Estrogen Combinations. *Acta Psychiatrica Scandinavica*, **Supplementum 236** (1972).

earlier studies (*i.e.*, studies predating 1972) are cited. It must be noted that these studies were conducted with the much higher-dose oral contraceptive preparations that were used in the 1960's, and were trying to demonstrate whether certain formulations could ameliorate premenstrual symptoms that these early contraceptive preparations were said to have exacerbated. At that, the studies cited in this table indicate that persons taking oral contraceptives were more likely, not less likely, to have mood or sexual disturbances. Section 2.6 summarizes this as follows:

> (g) Several studies show that gestagen dominated o.c. give adverse mental [mood] reactions in contrast to preparations with estrogen dominance. Only one study favours the opposite view.
>
> (h) In spite of several double blind investigations the basic problem cannot be said to have been satisfactorily answered, *i.e.*, whether and to what extent estrogens and progestagens exert any measurable influence upon mental functioning. ...

In fact, that is the reason that the study described in the instant publication was undertaken. Accordingly, this study examined mood changes (chapter 7, pp. 35-41), "menstrual symptoms" (chapter 8, pp. 42-44), and specific somatic symptoms (chapter 9, pp. 45-49). It then did some substantial cross-analysis of these symptoms and of the placebo effect (chapters 10-13, pp. 49-61). If this study had any consistent results, it would be that medicated subjects had a dysphoric reaction to medication more frequently than the placebo subjects (14-18% greater,

$p < 0.05$)(p. 34).

The Dennerstein paper authors indicate that use of micronized progesterone alleviated premenstrual symptoms. However, this study also had a number of limitations. First, the study had only 23 patients completing the trial. It is true that a greater number of subjects might have increased the statistical significance of the results. Yet comparing

the results of Table II (first month of treatment) to those of Table III (mean values of two months of treatment[3]), it is not at all certain that this would have been the case: In Table II, 7 measures showed statistically significant improvement and 18 did not, while in Table III, 4 measures showed statistically significant improvement, while 21 did not. (Summary variables were excluded in the above.) And in Table III, only one of the four measures with statistical significance was a psychological measure; the others were physical measures, which are not relevant to the diagnosis of PMDD.

Further, the hypothesis of these authors was that premenstrual symptoms were caused by an imbalance between estrogen and progesterone (see p. 618, second full paragraph). Accordingly, the study was specifically not designed to study the effects of administering both an estrogen and a progestogen together, as in an oral contraceptive.

Finally, in using micronized progesterone, the authors were using a compound that was more likely to work than the synthetic progestins used in oral contraceptives. Importantly, natural progesterone is not available in any contraceptive that has been marketed as such in the United States (or anywhere else). Thus, the authors can conclude, "further studies are needed to determine the optimum duration of treatment" (p. 1621). At the same time, the most one skilled in the art would be able to say following this study is that it would be worthwhile to test synthetic progestins, and perhaps combination oral contraceptives, to see if they work as well as progesterone.

2. Papers between 1983 and 1995

Accordingly, and appropriately, this question was studied a number of times in following years. Some examples follow:

[3] This notwithstanding the title on Table III, p. 1620. See p. 1619, first complete paragraph.

In 1983 (before the Dennerstein paper), Gaspard, *et al.*, published on a then-new triphasic oral contraceptive studied in 75 women. This contraceptive contained the "lowest quantity of steroids of all [then-]available preparations." Based on the previous work cited above, the result of this study was that "no increases in dysmenorrhoea and/or premenstrual tension were noted."[4]

Walker and Bancroft (1990) studied differences between a monophasic OC group (n = 35), a triphasic OC group (n = 30) and a nonsteroidal contraceptive group (n = 57) in premenstrual symptoms. The only symptom measured that was improved in the active groups was breast tenderness (in the monophasic group only). In the monophasic group, there was also some delay in symptomatology from premenstrual to menstrual, but not a lessening of symptoms.[5] The follow-up study from 1993 compared 276 oral contraceptive users and 276 non-users, all of whom were self-described PMS sufferers, on measures of mood, clumsiness, food craving and other symptoms. When controlling for the severity of premenstrual depression or menstrual pain, there was no difference between the monophasic contraceptive group, the triphasic contraceptive group and the non-OC group in mood, food craving, or clumsiness. There was an improvement in the physical measures of menstrual pain and premenstrual breast tenderness in the contraceptive users, as well as some delay from premenstrual to menstrual in the monophasic group.[6]

Backstrom, *et al.* (1992), studied 37 women in a single-blinded comparison of a monophasic and a triphasic oral contraceptive, each containing desogestrel. Both contraceptives helped treat premenstrual symptoms. However, there was no placebo group in this study. Given the already well-known placebo effect in this area (*cf.*, for example, Gullberg, in chapter 13,

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[4] UJ Gaspard, JL Deville, M Dubois. Clinical experience with a triphasic oral contraceptive ('Trinordiol') in young women. *Curr Med Res Opinion*, **8(6)**:395-404 (1983). Emphasis by the authors of the Declaration.

[5] A Walker and J Bancroft. Relationship between premenstrual symptoms and oral contraceptive use: a controlled study. *Psychosomatic Medicine*, **52(1)**:86-96 (1990).

[6] J Bancroft and D Rennie. The impact of oral contraceptives on the experience of premenstrual mood, clumsiness, food craving and other symptoms. *Journal of Psychosomatic Research*, **37**:195-202 (2003).

p. 61), one could not conclude from this study that these contraceptives work differently from placebo.[7]

Andolsek (1992) published results of one of the Ortho Tri-Cyclen open-label Phase III trials, n = 1,783. This was not a PMS or PMDD trial, but the author notes that "only minimal and statistically and clinically insignificant variations in menstrual flow, dysmenorrhea, and premenstrual tension occurred.[8]

Graham and Sherwin published two papers (1992 and 1993) on a study of 45 women getting a triphasic OC or placebo. In this study, both active and placebo groups showed improvement on a variety of measures, but there was no difference between active and placebo. Premenstrual breast pain and bloating were significantly reduced with active treatment compared to placebo ($p < 0.03$).[9] Notwithstanding the mood improvement in both active and placebo groups, there was a reduction in sexual interest in the OC group.[10]

Accordingly, by 1995, one of the earlier review articles specifically covering PMDD stated,

> Thus, the evidence in the majority of studies suggests that neither natural nor synthetic progesterone is efficacious in treating symptoms of [PMDD].[11] ...
>
> Although numerous uncontrolled studies have reported a reduction in a variety of [PMDD] *symptoms* in women using oral contraceptives (OCs), only two investigations more specifically address patients with [PMDD]; neither uses formal [PMDD] criteria. In one, which involved women who considered themselves to suffer from [PMDD], a subjects taking OCs had more-severe [PMDD] symptoms than did those who were not using them. In the other, a double-blind, placebo-controlled investigation of women with [PMDD], a triphasic OC had neither beneficial nor negative effects on mood as compared with placebo. Thus, it remains uncertain whether OCs mitigate or exacerbate the

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[7] T Backstrom, Y Hansson-Malmstrom, BA Lindhe, B Cavalli-Bjorkman, S Nordenstrom. Oral contraceptives in premenstrual syndrome: a randomized comparison of triphasic and monophasic preparations. *Contraception*, **46**:253-68 (1992).

[8] KM Andolsek. Cycle control with triphasic norgestimate and ethinyl estradiol, a new oral contraceptive agent. *Acta Obstet Gynecol Scan.*, **Supplement to 156**:22-6 (1992).

[9] CA Graham, BB Sherwin. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res.* **36(3)**:257-66 (1992).

[10] CA Graham, BB Sherwin. The relationship between mood and sexuality in women using an oral contraceptive as a treatment for premenstrual symptoms. *Psychoneuroendocrinology*, **18(4)**:273-81 (1993).

[11] The authors of this review cite the Dennerstein paper but dismiss it as a finding contrary to most other studies.

> symptoms of PMDD. They have been associated with worsening of depressive symptoms in two of three double-blind studies. Depressed mood has been associated with the use of OCs in up to 50% of women taking them, and women with a history of depression appear to be particularly at risk. These agents should be used cautiously, if at all, in women with [PMDD] and a prior history of depression.[12]

Thus the state of the art, as of 1995 and onward, was that progestins and oral contraceptives might alleviate some physical symptoms of PMS, most notably breast tenderness, but that they had no effect on the psychological symptoms which must be present for a diagnosis of PMDD.

Conclusion

By the time of the filing of this patent, there was existing art as to the idea of attempting to treat premenstrual symptoms of various types with oral contraceptive preparations. However, it is equally true that by the time of the filing of this patent, the evidence strongly suggested to those skilled in the art that oral contraceptives had no benefit in treating the psychological symptoms required in a diagnosis of PMDD. (In fact, the only premenstrual symptom about which there was a settled benefit was breast tenderness, not a PMDD issue).

Accordingly, the benefit demonstrated in applicants' data on oral contraceptives containing drospirenone would be unexpected, and therefore patentable.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States

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[12] LL Altshuler, V Hendrick and B Parry. Pharmacological Management of Premenstrual Disorder. *Harvard Review of Psychiatry*, 5:233-45 (1995).

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1/26/05
DATE

Dr. Marie L. Foegh